
Meerwein Reaction of Phosphonium Ions with Epoxides and Thioepoxides in the Gas Phase

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Phosphonium ions are shown to undergo a gas-phase Meerwein reaction in which epoxides (or thioepoxides) undergo three-to-five-membered ring expansion to yield dioxaphospholanium (or oxathiophospholanium) ion products. When the association reaction is followed by collision-induced dissociation (CID), the oxirane (or thiirane) is eliminated, making this ion molecule reaction/CID sequence a good method of net oxygen-by-sulfur replacement in the phosphonium ions. This replacement results in a characteristic mass shift of 16 units and provides evidence for the cyclic nature of the gas-phase Meerwein product ions, while improving selectivity for phosphonium ion detection. This reaction sequence also constitutes a gas-phase route to convert phosphonium ions into their sulfur analogs. Phosphonium and related ions are important targets since they are commonly and readily formed in mass spectrometric analysis upon dissociative electron ionization of organophosphorous esters. The Meerwein reaction should provide a new and very useful method of recognizing compounds that yield these ions, which includes a number of chemical warfare agents. The Meerwein reaction proceeds by phosphonium ion addition to the sulfur or oxygen center, followed by intramolecular nucleophilic attack with ring expansion to yield the 1,3,2-dioxaphospholanium or 1,3,2-oxathiophospholanium ion. Product ion structures were investigated by CID tandem mass spectrometry (MS^2) experiments and corroborated by DFT/HF calculations. (J Am Soc Mass Spectrom 2004, 15, 398–405) © 2004 American Society for Mass Spectrometry

Organophosphorous compounds are important owing to their agricultural and industrial applications, for example, as pesticides and additives in plasticizers [1]. Their trace analysis is also of concern since they are used as potent chemical warfare agents [2]. The latter application has motivated the development of methods for their fast and accurate trace identification and quantification. Since false positives must be avoided, the requirement of very high selectivity is usually met using tandem mass spectrometry (MS^2), which allows short analysis times in combination with low-level detection. Gas-phase reactions in a mass spectrometric environment have proven to be an excellent method of rapid, sensitive, and particularly selective chemical analysis for warfare agents [3, 4]. Collision-induced dissociation (CID) remains, however, by far the most common method of implementing the change in mass/charge ratio needed to perform an MS^2 experiment, and thus, to improve selectivity. In this

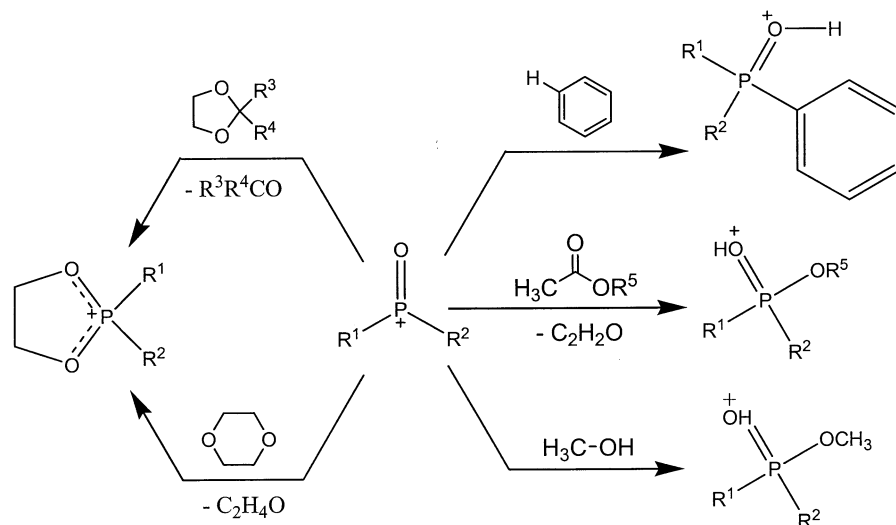
study, selective ion/molecule reactions are used for reliable trace detection of organophosphorous esters. Experiments focus on the phosphonium ions, $CH_3P(O)OCH_3^+$ (m/z 93) and $CH_3OP(O)OCH_3^+$ (m/z 109), the main fragments of the nerve agent simulant, dimethyl methylphosphonate (DMMP).

Scheme 1 summarizes the principal ion/molecule reactions known for phosphonium ions [4–9]. Transacetalization of phosphonium ions with 1,4-dioxane has recently been used to identify the warfare agent simulant, DMMP, with enhanced selectivity [5]. The reaction is known to cause C–O by P–O bond replacement in cyclic acetals, and its potential application to the identification of chemical warfare agents was pointed out some time ago [6, 7]. The phosphonium ion, aromatic compounds $CH_3OP(O)OCH_3^+$, reacts with benzene by electrophilic addition, and under CID conditions the adduct loses a methanol molecule [8]. Phosphonium ions undergo addition with methanol [9], while methoxyl abstraction [10] occurs when reacting with methyl esters.

Phosphonium and acylium ions are structurally analogous and display related gas phase reactivity. Recent multiple-stage mass spectrometric studies have

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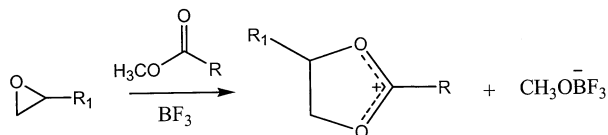
Scheme 1

systematically investigated the intrinsic reactivity of mass-selected gaseous acylium ions and have demonstrated synthetic and analytical applications of these reactions [12–26]. Gaseous acylium ions undergo the following reactions: polar $[4 + 2^+]$ cycloaddition with dienes [11, 12], ketalization with diols and analogs [13, 14], and transacetalization with five- and six-membered cyclic acetals [15–20] or with seven-membered acetals. Acylium ions also promote ring contraction [21] and sequential cyclization of acylium ions with two nitrile molecules, yielding 1,3,5-oxadiazinium ions [22]. In earlier work, the gas-phase Meerwein reaction of acylium ions with epoxides and thioepoxides to yield cyclic 1,3-dioxolanylium ions was first reported [23]. Halogen (X) acylium ions, $X\text{-CO}^+$ ($F > Cl > Br$), promote carbonylation of benzene [24, 25] and of five-membered heterocyclics via selective functionalization of their inert C–H aromatic bonds. Gaseous acylium ions also react with neutral peptides by *N*-terminal derivatization followed by dissociation that produces structurally-diagnostic, modified b_1 sequence ions [26]. The benzoyl cation, PhCO^+ , reacts with amines (M) to yield characteristic $[\text{M} + \text{PhCO}]^+$, $[\text{M} + \text{NH}_2\text{R}]^+$, and $[\text{PhCONH}_3]^+$ product ions in proportions that are characteristic of the amine [27, 28]. Acylium ions also react with isomeric α -, β - and γ -hydroxyketones via structurally diagnostic cyclization reactions [29] and with α,β -unsaturated carbonyl compounds by single and double $[4 + 2^+]$ Diels-Alder cycloaddition [30]. Recently, reactions of acylium ions were performed in-source under selected electrospray and atmospheric pressure chemi-

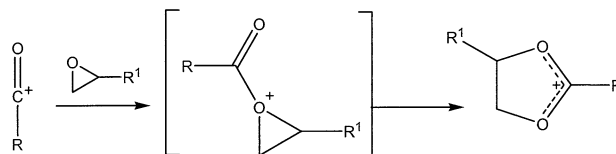
cal ionization conditions and used as a structurally diagnostic test for relatively large cyclic acetals of synthetic importance [31].

The known reactions of gaseous acylium ions indicated above are candidates for identification of phosphonium ions because of their expected similar reactivity. However, many of these reactions have not yet been tested for phosphonium ions. An example of this is the ring-expansion Meerwein reaction with epoxides and thioepoxides [23]. Meerwein first reported his eponymous reaction in 1955 as a ring-expansion reaction occurring in a solution of epoxides and esters in the presence of BF_3 (Scheme 2) [32].

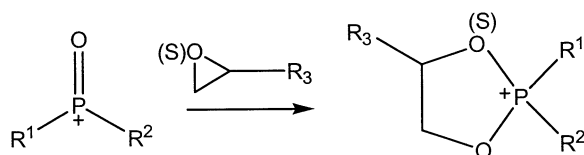
Recently, it has been reported [23] that this reaction also occurs readily in the gas phase for acylium ions (RCO^+), which is probably the key ionic intermediate in solution. The reaction appears to proceed by initial O(S)-acylation and intramolecular nucleophilic attack, which yields cyclic 1,3-dioxolanylium ions after three- to five-membered ring expansion (Scheme 3). Reaction with silaformyl anion, HSiO^- [33], has been studied in detail and shows rearrangements involving Si–O and Si–S bond formation [34]. Here we report a systematic study of the analogous reaction of phosphonium ions with a variety of epoxides and thioepoxides (Scheme 4). Product structures are proposed based on CID experiments and on theoretical HF/DFT calculations.



Scheme 2



Scheme 3



Scheme 4

Experimental

Ion/molecule reactions were performed using a Finnigan TSQ-70 triple quadrupole mass spectrometer (Thermo Finnigan Corporation, San Jose, CA) fitted with an EI/CI ion source. The manifold and ion source temperatures were maintained at 150 °C and 70 °C, respectively. The $\text{CH}_3\text{P}(\text{O})\text{OCH}_3^+$ (or $\text{CH}_3\text{OP}(\text{O})\text{OCH}_3^+$) ions were generated by 70 eV electron ionization (EI) of DMMP (Lancaster, Pelham, NH) [35] and trimethyl phosphate [36]. Ion/molecule reactions were performed by mass selecting the precursor ions in Q1, reacting these ions with the neutral reagent in Q2, and then mass analyzing the product ions in Q3. Ethylene sulfide 1 (Aldrich Chemical Company, Inc., Milwaukee, WI), propylene sulfide 2 (Aldrich), propylene oxide 3 (Aldrich), and 3,4-epoxy-1-butene 4 (Aldrich) were used as collision gases, and the optimized collision energy was found to be nominally 0 eV. For the CID (MS^2) experiments, a product ion formed by ion/molecule reaction in the ion source was mass-selected by Q1 and further dissociated in Q2 by 10 eV CID with argon, while scanning Q3 to acquire the spectra. The 10 eV collision energy was taken as the voltage difference between the ion source and the collision quadrupole, and the indicated pressures in each differentially pumped region were typically 8×10^{-6} torr (Q2) (1 torr = 133.3 Pa). Optimized geometries and energies of idealized conformations were obtained by theoretical calculations with no symmetry constraints using Becke3LYP [37–39] DFT/HF hybrid functionals and 6–311++G(d,p) basis sets as implemented in Gaussian 98 [40], and the displayed energies are with no ZPE correction. (Supplementary material of the optimized structures and transitional states are available from the authors upon request.)

Results and Discussion

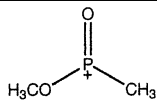
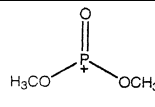
Mass-Selected Ion/Molecule Reactions

Table 1 summarizes the outcome of the reactions of the two phosphonium ions (Phos^+) with neutral epoxides and thioepoxides. The $\text{CH}_3\text{P}(\text{O})\text{OCH}_3^+$ ion (m/z 93) and the $\text{CH}_3\text{OP}(\text{O})\text{OCH}_3^+$ ion (m/z 109) were formed by EI of DMMP and trimethyl phosphate, respectively. Each ion was individually mass-selected and reacted at low energy collision conditions (near zero eV) with two model epoxides (propylene oxide and 3,4-epoxy-1-butene) and two model thioepoxides (ethylene sulfide and propylene sulfide).

Figure 1 shows, as a typical example, the product ion mass spectrum for the reaction of $\text{CH}_3\text{P}(\text{CO})\text{OCH}_3^+$ (m/z 93) with ethylene sulfide. The Meerwein product ion is seen at m/z 167 (Figure 1). Evidence that this ion is the five-membered cyclic product and not a simple adduct is provided below. Competitive reactions giving signals in the mass spectrum include the following: proton transfer, forming protonated propylene sulfide (m/z 75), the second most abundant product observed, and formation of the propylene sulfide proton-bound dimer (m/z 149). Competitive reactions also form the m/z 63 ion, which arises from CID of the reactant ion, [41] and the m/z 111 ion, which is the adduct of the reactant ion with water. Water is likely a contaminant of the liquid neutral precursors used to form the phosphonium ions. The m/z 111 ion probably dissociates to $\text{CH}_3\text{OP}(\text{OH})^+$ (m/z 79) by methanol loss, whereas the presence of the m/z 109 ion indicates dissociation (to a minor extent) of the Meerwein product ion at m/z 167 (see the MS/MS section below), even under the low energy collision conditions used to favor association reactions. Although acylium ions are known to abstract hydride quite efficiently from propylene sulfide [23], no hydride abstraction is observed in reactions with $\text{CH}_3\text{P}(\text{O})\text{OCH}_3^+$.

Phosphonium ions are found to display similar reactivity with thioepoxides to the behavior noted for the acylium ions studied earlier [23]. However, the current study indicates that the phosphonium ions do not react readily with epoxides, as evidenced here by attempted reactions with two model epoxides. This behavior is in

Table 1. Major product ions [m/z (relative abundances)] for reactions of mass-selected phosphonium ions (Phos^+) with epoxides and thioepoxides (M)

Reactant ion						
	MPhos ⁺	MH ⁺ , M ₂ H ⁺	[M – H] ⁺	MPhos ⁺	MH ⁺ , M ₂ H ⁺	[M – H] ⁺
(1) Ethylene sulfide	153 (30)	61 (100)	None	169 (40)	61 (30)	59 (5)
(2) Propylene sulfide	167 (80)	75 (95)	None	183 (20)	75 (100), 149 (65)	73 (10)
(3) Propylene oxide	None	59 (70)	57 (15)	None	59 (50)	57 (60)
(4) 3,4-epoxy-1-butene	163 (5)	71 (45)	69 (5)	169 (3)	71 (60)	69 (5)

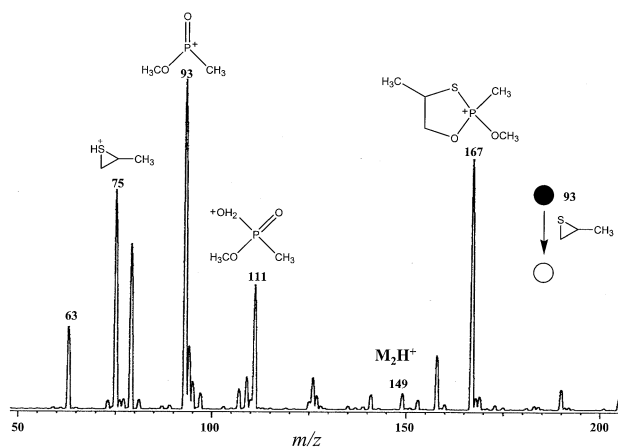


Figure 1. Product ion mass spectrum for the reaction of $\text{CH}_3\text{P}(\text{O})\text{OCH}_3^+$ (m/z 93) with propylene sulfide. Note the abundant Meerwein product ion at m/z 167.

contrast with that observed with the acylium ions that react with both oxiranes and thiiranes. For phosphonium ions, proton transfer and hydride abstraction dominate, and only a minor Meerwein product is observed for the oxirane 3,4-epoxy-1-butene. This distinctive behavior of phosphonium ions toward epoxides can be ascribed to the less effective molecular orbital overlap between oxygen and phosphorus atoms and the greater phosphonium ion acidity that favors the competitive proton transfer reaction.

The Meerwein reactivity of the two phosphonium

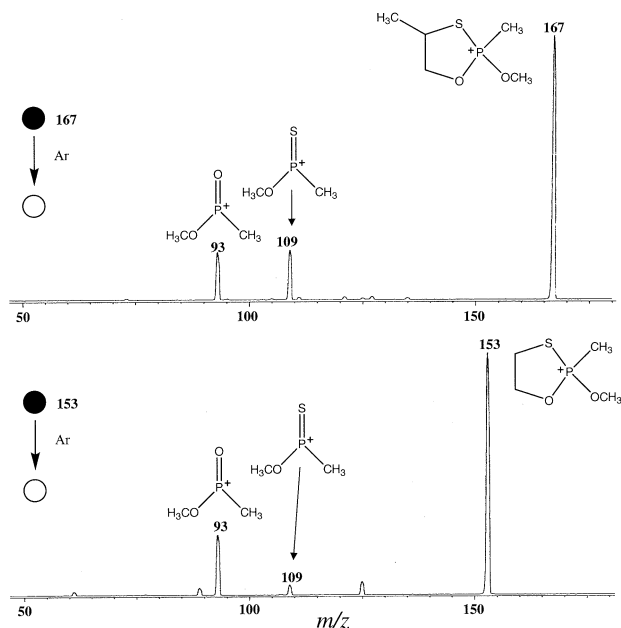
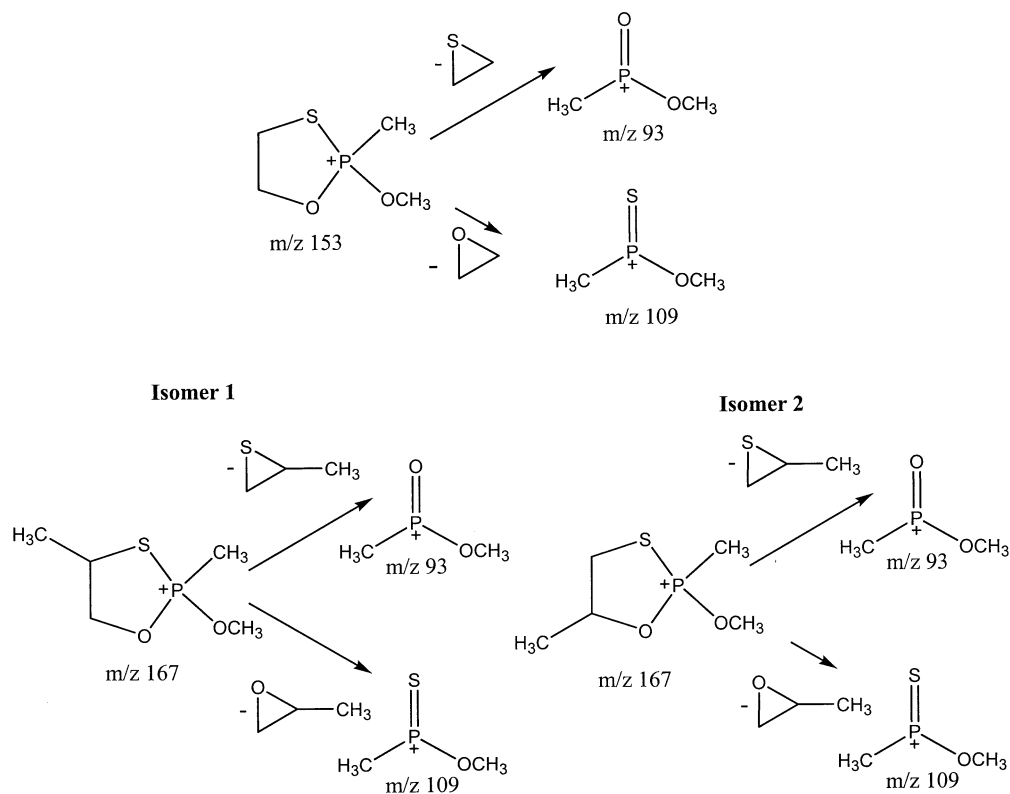
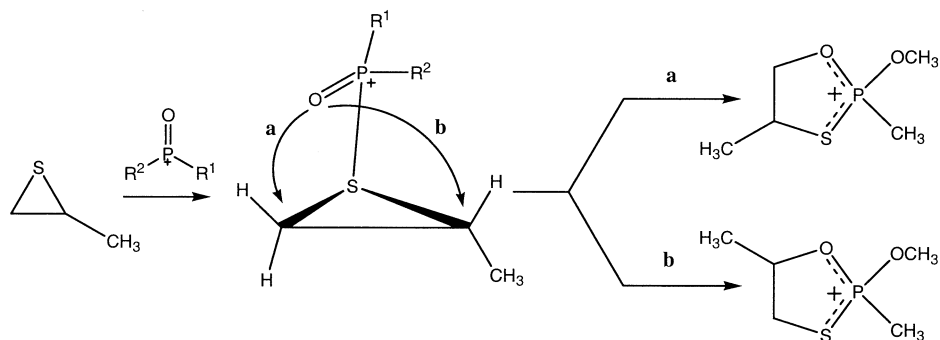


Figure 2. Product ion (CID) mass spectrum of the adduct generated upon in-source reaction of the ion (m/z 93) with (a) propylene sulfide and (b) ethylene sulfide.

ions studied here is rather similar. The $\text{CH}_3\text{OP}(\text{O})\text{OCH}_3^+$ ion is slightly more reactive, particularly towards the thioepoxides **1** and **2**, whereas the $\text{CH}_3\text{OP}(\text{O})\text{OCH}_3^+$ ion is, in general, more prone to



Scheme 5



Scheme 6

undergo competitive hydride abstraction. The lack of reactivity of phosphonium ions with epoxides **3** and **4** further emphasizes the specificity of the reaction with thioepoxides.

CID Experiments

To help elucidate product ion structures, and to verify the possibility of further improving the selectivity, all product ions of the Meerwein reaction were mass-selected and then subjected to CID experiments (Figure 2). The dissociation of the adduct at m/z 153, formed when $\text{CH}_3\text{P}(\text{O})\text{OCH}_3^+$ reacts with ethylene sulfide, shows a dissociation pattern (Figure 2b) which indicates that the product ion is cyclic. The ion dissociates back to both the reactant ion at m/z 93, by ethylene sulfide loss, and also to the thiophosphonium ion at m/z 109, by ethylene oxide loss, with dissociation to m/z 93 more favored. Note that O-by-S replacement in the reactant ion has been achieved in the ion/molecule reaction-

dissociation sequence and that such O-S replacement provides good evidence for the cyclic nature of the Meerwein product ion. This O-S replacement was also observed for the Meerwein product of the reaction of ethylene sulfide with acylium ions, in which CID of the adduct produces both the reactant acylium ion and its sulfur analog, but the acylium ion was favored to a much greater extent. The efficiency of O-C orbital overlap compared with S-C overlap accounts for this result.

When interpreting the dissociation of the Meerwein product of the reaction of $(\text{CH}_3)_2\text{NCS}^+$ with propylene oxide, the 5-methyl group was proposed to facilitate cleavage of the vicinal C-S bond in the adduct [23]. Based on the same reasoning, the methyl group in the 5-position (Scheme 5, Isomer 1) should facilitate cleavage of the vicinal C-S bond, and hence, promote the loss of propylene oxide. This effect causes an inversion in the abundance ratio compared to the unsubstituted ion, which preferentially forms the fragment thio-phosphonium ion at m/z 109 (Scheme 5).

The Meerwein reaction of the phosphonium ions with propylene sulfide may generate two isomeric cyclic products, **1** and **2** (Scheme 6). Formation of a major isomer in the reaction of acylium ions with propylene sulfide has been proposed based on experimental data and theoretical calculations. For reactions of phosphonium ion with propylene sulfide, Isomers **1** and **2** of m/z 167 could be formed depending on the steric effect and/or molecular efficiency of the orbital overlap between the oxygen atom from the phosphonium moiety with either one of the two electrophilic carbons on the thioepoxy moiety (Scheme 6). Similar to the situation for acylium ions, intramolecular attack by the oxygen likely occurs preferentially on the more substituted carbon yielding m/z 167 (Scheme 5).

The dissociation of the Meerwein product for the reaction of $\text{CH}_3\text{OP}(\text{O})\text{OCH}_3^+$ with ethylene sulfide shows similar dissociation patterns (Figure 3). Again, isomer **1** is likely formed upon reaction with propylene sulfide, which considerably enhances the relative abundance of m/z 125 over that of m/z 109 (Scheme 5).

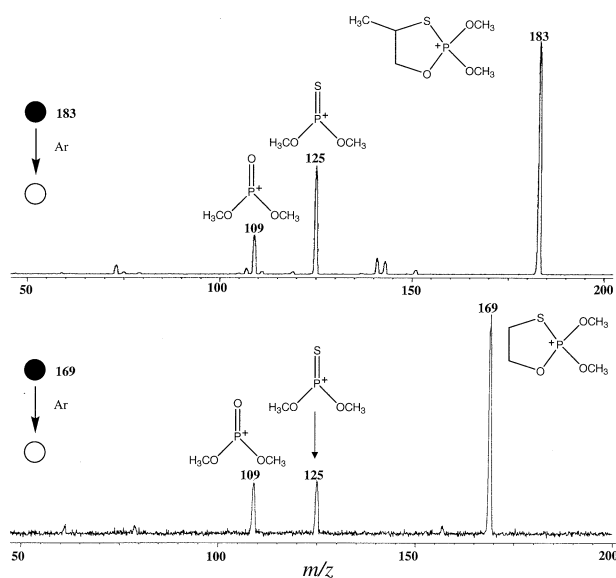


Figure 3. Product ion (CID) mass spectrum of the adduct ions (m/z 183 and 169) generated upon in-source reaction of the ion (m/z 109) with (a) propylene sulfide and (b) ethylene sulfide.

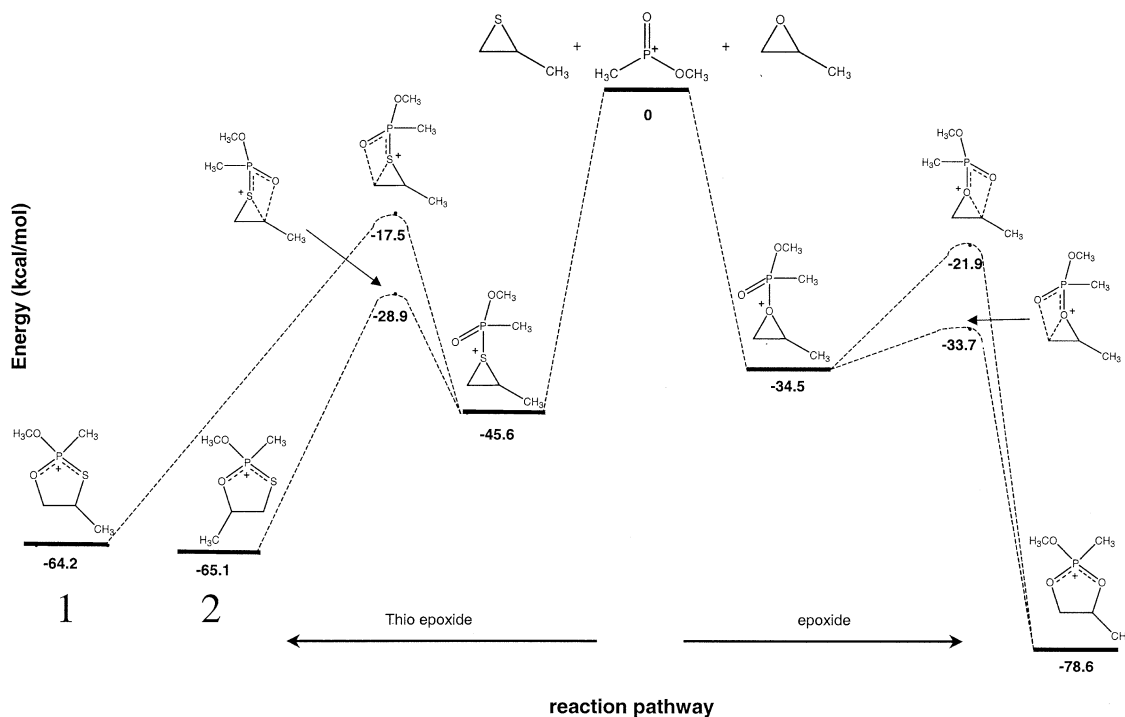


Figure 4. HF/DFT B3LYP/6-311 + G(d,p) potential energy surface diagram for the three-to-five-membered ring expansion Meerwein reaction of $\text{CH}_3\text{P}(\text{O})\text{OCH}_3^+$ with propylene oxide or propylene sulfide. All transition states were characterized by a negative imaginary frequency, $\text{TS1}_{\text{propylenesulfide}}$ (-252 cm^{-1}), $\text{TS2}_{\text{propylenesulfide}}$ (-413 cm^{-1}), and $\text{TS}_{\text{propyleneoxide}}$ (-466 cm^{-1}). The energy of the full geometry optimized species are, in hartrees: $\text{CH}_3\text{P}(\text{O})\text{OCH}_3^+$ (-571.446982), propylene sulfide (-516.159521), $\text{TS1}_{\text{propylenesulfide}}$ (-1087.652467), $\text{TS2}_{\text{propylenesulfide}}$ (-1087.634350), 1,3,2-oxathiophospholanium Isomer 2 (-1087.710164), 1,3,2-oxathiophospholanium Isomer 1 (-1087.708743), propylene oxide (-571.446982), $\text{TS}_{\text{propyleneoxide}}$ (-764.650278), and 1,3,2-dioxaphospholanium (-764.740530).

DFT/HF Calculations (Reactions Enthalpies)

Figure 4 shows a potential energy surface diagram, with key intermediates and transition states, for the gas-phase Meerwein reaction of $\text{CH}_3\text{P}(\text{O})\text{OCH}_3^+$ with both propylene oxide and propylene sulfide. The overall reactions are both highly exothermic, by -78.6 kcal/mol in the case of the epoxide (formation of the 1,3,2-dioxaphospholanium ion) and by either -64.2 kcal/mol or -65.1 kcal/mol in the case of the thioepoxide (formation of two isomeric 4-methyl and 5-methyl-1,3,2-oxathiophospholanium ions). The key transition states and intermediates are far below the energy of the reactants. Hence, after the rate-determining association collision, the pathways to the cyclic products are all thermodynamically accessible (downhill), owing to excess internal energy acquired during the initial, rather exothermic (S)O-addition.

Even though the reaction of $\text{CH}_3\text{P}(\text{O})\text{OCH}_3^+$ with propylene oxide is shown, by itself, to be thermodynamically accessible, the experimental data shows no Meerwein product ion; instead, proton transfer dominates (Table 1). It is, therefore, likely that the competitive proton-transfer reaction is far more (kinetically) favored, and hence much faster than the Meerwein reaction. Reaction of $\text{CH}_3\text{P}(\text{O})\text{OCH}_3^+$ with propylene sulfide is also highly exothermic, but here, competitive

reactions are less successful. For the thioepoxides examined, the gas-phase Meerwein reaction is both thermodynamically and kinetically favored over the competitive reactions of proton transfer and hydride abstraction.

Chemical Analysis

The gas-phase Meerwein reaction, particularly when performed with collision-induced dissociation of product ions, is an attractive, highly structurally diagnostic method that should enhance selectivity for the trace detection of DMMP and other phosphonates. The use of propylene sulfide provides extra selectivity for detection/characterization of the parent phosphorus compounds through the oxygen-for-sulfur replacement in the ion/molecule reaction/CID sequence.

This prediction was tested by performing chemical ionization on a mixture of DMMP and trimethyl phosphate and recording a constant neutral gain of 16 spectrum [42]. The methyl-thiirane was introduced into the collision quadrupole, and the collision energy was chosen so as to allow both ion/molecule reactions and CID. The spectrum showed only two signals, corresponding to the expected sulfur-for-oxygen replace-

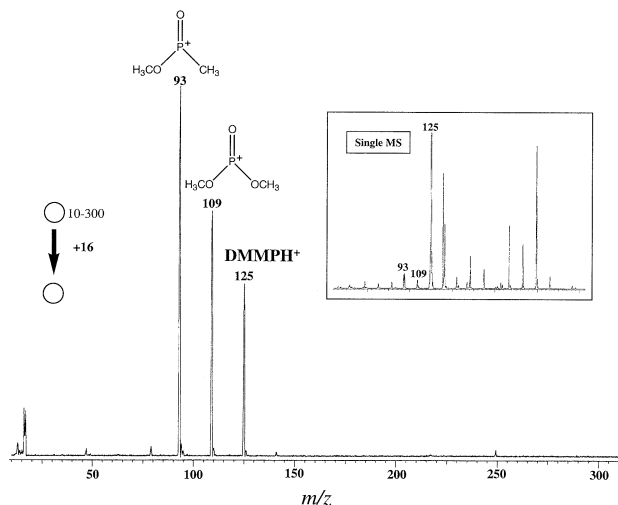


Figure 5. Constant neutral gain MS/MS spectrum of a mixture of methyl trimethylacetate and DMMP, after electron ionization. Methyl-thiirane is used as the neutral collision gas, and Q1 is scanned from 10 to 300 Th. Q3 scans the corresponding product ions. The mass/charge offset is set as 16 Th. The inset is the single mass spectrum of the mixture of methyl trimethylacetate and DMMP.

ments in the phosphonium ions m/z 93, m/z 109, and m/z 125 (Figure 5, Scheme 5). The m/z 125 ion, protonated DMMP, is observed in the spectrum because of its dissociation and the further reaction of the fragment ions (m/z 93 and 109) with methylthiirane.

Conclusion

A novel, structurally diagnostic gas-phase ion/molecule reaction for phosphonium ions is reported. The Meerwein reaction occurs with epoxides and, more efficiently, with thioepoxides. The reaction proceeds by (S)O phosphonium ion addition to the (thio)epoxide, followed by intramolecular nucleophilic attack that results in three- to five-membered ring expansion, forming 1,3,2-dioxaphospholanium or 1,3,2-oxathio-phospholanium ions. The greater nucleophilicity and enhanced S–P orbital overlap accounts for the fact that the Meerwein reaction competes favorably, thermodynamically, and kinetically, with proton transfer and hydride abstraction. The two phosphonium ions investigated here are important target ions, as they are abundant in the electron ionization spectra of a variety of organophosphorous chemicals.

Acknowledgments

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